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Congenital myopathies: not only a Paediatric topic

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ABSTRACT (200 words)

Purpose of review: This article reviews adult presentations of the major congenital myopathies - Central Core Disease (CCD), Multi-minicore Disease (MmD), Centronuclear Myopathy (CNM) and Nemaline Myopathy (NM) - , with an emphasis on common genetic backgrounds, typical clinico-pathological features and differential diagnosis.

Recent findings: The congenital myopathies are a genetically heterogeneous group of conditions with characteristic histopathological features. Whilst essentially considered Paediatric conditions, some forms – in particular those due to dominant mutations in the skeletal muscle ryanodine receptor (*RYR1*), the dynamin 2 (*DNM2*), the amphiphysin 2 (*BIN1*) and the Kelch Repeat-and BTB/POZ Domain-Containing Protein 13 (*KBTD13*) gene – may present late into adulthood. Moreover, dominant *RYR1* mutations associated with the malignant hyperthermia susceptibility (MHS) trait have been recently identified as a common cause of (exertional) rhabdomyolysis presenting throughout life. In addition, improved standards of care and development of new therapies will result in an increasing number of patients with early-onset presentations transitioning to the adult neuromuscular clinic. Lastly, if nemaline rods are the predominant histopathological feature, acquired treatable conditions have to be considered in the differential diagnosis.

Summary: Recently identified genotypes and phenotypes indicate a spectrum of the congenital myopathies extending into late adulthood, with important implications for clinical practice.

KEY WORDS: (5 key words)

Congenital myopathies; adult presentations; skeletal muscle ryanodine receptor (*RYR1*) gene; exertional rhabdomyolysis; late-onset axial myopathy

INTRODUCTION *(Total word count main text – 2485 words)*

The major congenital myopathies - Central Core Disease (CCD), Multi-minicore Disease (MmD), Centronuclear Myopathy (CNM), and Nemaline Myopathy (NM) – are a clinically and genetically heterogeneous group of neuromuscular disorders with characteristic but not always specific histopathological features (for review, [1]).

Common clinical features include pronounced truncal and proximal weakness, and although it is often not possible to make a tentative diagnosis on clinical grounds alone, for example additional extraocular, distal or respiratory muscle involvement may provide important clues as to the underlying genetic defect (Table 1). Orthopaedic manifestations including scoliosis or ligamentous laxity are common. Although severity is highly variable, many of these conditions remain stable or are only slowly progressive over prolonged periods.

Mutations in more than 15 genes have been implicated to date, encoding proteins with (putative) roles in calcium homeostasis and excitation-contraction coupling (ECC), thin and thick filament assembly and interaction, and membrane trafficking. Mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene encoding RyR1, the principal sarcoplasmic reticulum (SR) calcium release channel, have been implicated to variable degrees in all major forms. In contrast to the congenital muscular dystrophies, integrity of the muscle cell is usually preserved, reflected in normal or only slightly elevated CK levels. Considering the complexities of the underlying genetics and clinical presentations, a coordinated multidisciplinary approach is essential [2, 3].

The congenital myopathies are often considered pre-eminently Paediatric conditions, and many adult neurologists may feel uncomfortable with their diagnosis and management. However, not all congenital myopathies are of early onset and may indeed present only in adulthood. Moreover, improvements in supportive care and development of novel therapies

are likely to substantially reduce morbidity and mortality, resulting in an increasing number of patients with early-onset myopathies transitioning to adult neuromuscular services [4]. Lastly, the *RYR1* gene has recently also been implicated in induced and episodic phenotypes such as (exertional) rhabdomyolysis (ERM) or periodic paralysis presenting throughout life. To highlight the relevance of the congenital myopathies for adult neuromuscular practice, this review will give an overview over the major entities, with a particular emphasis on late-onset presentations and induced and episodic phenotypes.

CONGENITAL MYOPATHIES WITH CORES – CENTRAL CORE DISEASE (CCD) AND MULTI-MINICORE DISEASE (MmD)

The “core myopathies” (for review, [5]) are the most common form of congenital myopathy [6, 7] and are most commonly associated with mutations in *RYR1*. *RYR1* mutations have recently emerged as the predominant genetic cause of non-dystrophic neuromuscular disorders, associated with dominantly inherited CCD [8, 9], and subgroups of recessively inherited MmD [10-12], CNM [13] and congenital fibre type disproportion (CFTD) [14]. The dominantly inherited Malignant Hyperthermia Susceptibility (MHS) trait (for review, [15]), a pharmacogenetic predisposition to severe and potentially life-threatening reactions in response to halogenated anaesthetics and muscle relaxants, is an allelic condition.

Although more severe presentations have been reported [16], dominantly inherited *RYR1*-related CCD (for review, [17]) (Figure 1E, Figure 2A) is characterized by mild to moderate proximal weakness pronounced in the hip girdle presenting from infancy or childhood. Orthopaedic manifestations such as congenital hip dislocation, scoliosis and generalized joint hypermobility are common. In contrast to recessive *RYR1*-related myopathies, extraocular muscle (EOM) involvement is not a feature, and bulbar, respiratory and in particular cardiac

involvement is uncommon. Myalgia may be prominent [18]. Mild symptoms present from childhood may not have been recognized as such [19], resulting in often long intervals between initial symptom manifestation and eventual diagnosis. CCD tends to be stable over long periods with possible progression later in life [20]. Considering marked intrafamilial variability, the diagnosis of CCD in a patient should prompt a careful review of the family history and assessment of other relatives.

RYR1-related MHS is allelic to CCD, and some patients with CCD may also be MH susceptible. Although the majority of MHS individuals are clinically asymptomatic unless exposed to potentially triggering agents, several permanent or induced neuromuscular manifestations appear to be specifically associated with MHS-related *RYR1* mutations. King-Denborough syndrome (KDS) [21], an early-onset myopathy with dysmorphic features, short stature, scoliosis and a predisposition to severe, occasionally unprovoked MH reactions, was recognized as a clinical entity by King and Denborough soon after their recognition of MHS [22]. More recently, (MHS-related) *RYR1* mutations have also emerged as a common cause of (exertional) rhabdomyolysis (ERM) (Figure 1A-B), accounting for up to 30% of ERM presentations in otherwise healthy individuals after other causes have been excluded [23]. ERM can clearly be provoked by unaccustomed exercise even in individuals without genetic predisposition; however, a predisposing genetic background has to be considered if such episodes are familial, recurrent, out of context to the exercise performed, or preceded by other (exercise-induced) muscle symptoms such as cramps, myalgia and weakness. *RYR1*-related rhabdomyolysis is commonly triggered by exercise, in particular in association with increased environmental temperatures, pyrexial illness, alcohol, medical or recreational drugs. Penetrance is low, with some individuals having had only one single episode despite an often intense exercise regime. In contrast to most metabolic causes, fasting does not appear to trigger *RYR1*-related rhabdomyolysis, and episodes may occur up to 72 hours after

exercise. *RYR1*-related rhabdomyolysis may mimic viral myositis [23, 24]. A recent case report indicates unaccustomed exercise before the triggering general anaesthesia as a contributory factor to MH [25], suggesting that MH may in fact be a multifactorial event and providing a potential explanation for its highly variable penetrance. Individuals with *RYR1*-related rhabdomyolysis are often particularly muscular and athletic [23, 26], making life style advice after a rhabdomyolysis event more challenging. Dantrolene given around exercise or at the onset of symptoms (unlabeled use) may safely prevent or ameliorate episodes without significantly affecting performance [26]. Allopurinol has also recently been suggested as a treatment for exercise-induced muscle damage (unlabeled use) [27]. Late-onset axial myopathy [28, 29] (Figure 1C-D), characterized by often progressive paravertebral muscle weakness and wasting in previously athletic and muscular individuals, is another neuromuscular manifestation of MHS-related *RYR1* mutations and shows clinical and genetic overlap with the ERM spectrum.

Recessive *RYR1*-related MmD [11] (Figure 1F-H, Figure 2B) is usually of earlier onset compared to dominantly inherited CCD and often characterized by more pronounced weakness and EOM involvement. The condition tends to be stable over time and most patients will transition to the adult neuromuscular clinic. One case has been reported presenting with features of atypical periodic paralysis presenting from adolescence [30].

Recessive *SEPNI*-related MmD [31], the second most common form of core myopathy, usually presents in childhood with spinal rigidity, scoliosis and early respiratory failure typically requiring non-invasive ventilation by the second decade. In contrast to the *RYR1*-related form, EOM involvement is not a typical feature. The condition tends to remain stable over prolonged periods, with marked discrepancy between profound respiratory impairment and often fully preserved ambulation.

Primary cardiomyopathies have been described in rarer forms of genetically distinct core myopathies. Amongst those, dominant mutations in *MYH7* may present with the typical clinico-pathological features of MmD in childhood but then develop features of Laing Distal Myopathy, an allelic condition [32, 33]. Recessive mutations in the giant *TTN* gene have been implicated in severe core myopathies with cardiac involvement [34] and may often feature a mixed pathology with additional fibre type disproportion and multiple internalized nuclei (see below). Considering frequent features of spinal rigidity, scoliosis and multiple contractures also involving the elbows, both *TTN*- and *MYH7*-related forms of core myopathies may mimic Emery-Dreifuss Muscular Dystrophy (EDMD). There is also overlap with the myofibrillar myopathy (MFM) spectrum [35] and *KBTD13*-related nemaline myopathy [36], which may feature cardiac involvement and additional cores on muscle biopsy (see below).

CONGENITAL MYOPATHIES WITH CENTRAL NUCLEI – X-LINKED MYOTUBULAR MYOPATHY (XLMTM) AND CENTRONUCLEAR MYOPATHY (CNM)

Centronuclear myopathies (CNMs) are characterized by the abundance of central nuclei on muscle biopsy (for review, [37, 38]). CNM has been associated with X-linked recessive mutations in *MTM1* encoding myotubularin [“X-linked myotubular myopathy (XLMTM)”] [39], autosomal-dominant mutations in *DNM2* encoding dynamin2 [40] and the *BIN1* gene encoding amphiphysin 2 [41], and autosomal-recessive mutations in *BIN1* [42], *RYR1* encoding the skeletal muscle ryanodine receptor [13], and *TTN* encoding titin [43]. Most genes implicated to date encode proteins implicated in membrane trafficking (for review, [44]).

Type 1 fibre predominance and atrophy are common histopathological features in all forms. In contrast to *MTM1*-, *DNM2*- and *BIN1*- related CNM, nuclei tend to be multiple internalized rather than strictly centralized in *RYR1*- and *TTN*-related CNM [13, 43]. Evolution of additional cores is particularly common in the *RYR1*-related form [45], and some patients may have marked fibre type disproportion [13]. A peculiar radial distribution of sarcoplasmic strands around central nuclei is a distinctive and consistent feature of *DNM2*-related CNM [40, 46-50], but has also been described in mild cases with dominantly inherited *BIN1*-related CNM; the latter form may also feature nuclear clustering. “Necklace fibres” have been reported in mild cases of XLMTM [51] and *DNM2*-related CNM [52].

XLMTM is the most common and the most severe form, with the majority of affected males not surviving beyond the first year of life unless fulltime ventilator support is provided [53]. However, a proportion may survive into adulthood without the need for longterm ventilation; the *MTM1* p.Glu157Lys mutation has been associated with a particularly mild phenotype [54]. Some XLMTM carriers may develop mild weakness [55], sometimes very late in life [56], but more severe manifestations in females are usually due to skewed X-inactivation or additional X-chromosomal abnormalities [57, 58]. There is a wide range of animal models of XLMTM with similar muscle pathology, summarized in a recent review [59].

Dominantly inherited *DNM2*-related CNM [40, 46, 60] is the form of CNM most likely to be encountered by an adult neurologist. Although more severe cases have been reported [46, 61], affected individuals typically present in adolescence or adulthood [60, 62-64], occasionally as late as the 6th decade. Exertional myalgia may be a presenting feature. Facial weakness, ptosis and EOM involvement are common but not universal. Jaw contractures are a feature in some patients [49, 65]. Muscle weakness is mainly proximal and axial, with frequent additional distal involvement [66-68] and, occasionally, marked muscle hypertrophy, particularly affecting the calves [52, 69]. Respiratory involvement is a feature in more severely affected

infants and may improve over time [46, 50, 61, 65]. Dominant intermediate CMTDIB [70] and axonal CMTM [71] are allelic conditions, and, although *DNM2* mutations implicated in CNM and CMT are distinct, there may be some clinical overlap in individual cases, as evidenced by frequently absent deep tendon reflexes and variable neurophysiological and neuropathological evidence for an associated mild neuropathy [49, 60, 64, 67, 68, 72]. An associated neuromuscular transmission defect and positive response to acetylcholinesterase inhibitors has been reported [73]. Additional multisystem involvement featuring neutropenia [52, 69] or cataracts [61, 74] has occasionally been observed. Muscle MRI may help to distinguish *DNM2*-related from other congenital myopathies [64, 66].

Dominant mutations in *BIN1*, previously associated with rare, recessively inherited severe CNM cases [42], have also been recently associated with a mild dominant form of CNM [41] (Figure 2C). Patients typically present later in adulthood with proximal weakness pronounced in the lower limbs, without significant respiratory impairment and only rarely extraocular muscle involvement. Muscle MRI may show additional distal muscle involvement.

RYR1-related CNM shares features with other recessive *RYR1*-related myopathies, in particular marked EOM involvement and a tendency to improve over time. EOM involvement is not a feature in *TTN*-related CNM; although cardiac involvement was not prominent in the original series [43], this ought to be monitored for considering the severe cardiac phenotypes in other *TTN*-related disorders.

CONGENITAL MYOPATHIES WITH NEMALINE RODS – NEMALINE MYOPATHY (NM)

Nemaline myopathy (NM) is one of the more common congenital myopathies and characterized by numerous nemaline rod bodies on muscle biopsy that appear red with the

Gömöri trichrome stain and are prominent in Toluidine Blue-stained semithin resin sections [for review, [75]]. To date, 10 genes have been linked to this disorder, including *ACTA1*, *NEB*, *TPM3*, *TPM2*, *CFL2*, *TNNT1*, *LMOD3*, *KBTBD13*, *KLHL40*, and *KLHL41*, of which recessive mutations in *NEB* and (*de novo*) dominant mutations in *ACTA1* are the most common (for review, [75]). NM is associated with highly variable degrees of muscle weakness, ranging from presentations within the fetal akinesia spectrum to only mildly affected adults.

NEB-related NM, the most common form, typically presents in infancy or childhood, often with disproportionate axial and bulbar involvement [76]. Scoliosis is common and respiratory involvement almost universal, despite preserved ambulation well into adulthood. Distal involvement in the lower limb becomes prominent over time and may be a presenting feature in some patients [77]. Although *ACTA1*-related NM is typically a profoundly severe condition [4, 78], rare patients may present in adulthood with respiratory failure but only little limb girdle weakness [79,80]. An associated cardiomyopathy is not a feature of *NEB*-related NM but has been rarely encountered in patients with *ACTA1* mutations [81,82]. An *ACTA1*-related progressive scapuloperoneal myopathy without nemaline rods on muscle biopsy [82] has been recently reported.

The form of NM most relevant to adult practice is the recently identified form due to dominant mutations in the *KBTBD13* gene (Figure 2D), or NEM6 [36] whose overall frequency is currently uncertain. NEM6 is characterized by a peculiar slowness of movements, and the development of slowly progressive muscle weakness affecting neck and proximal limb muscles. As in other adult-onset congenital myopathies, muscle weakness often manifests not until adolescence or adulthood, but all patients retrospectively report difficulties with sport in childhood [36, 84]. The characteristic slowness is often perceived as clumsiness, with patients generally unable to sprint or to suddenly adapt their position to

avoid falls. Respiratory insufficiency and cardiac abnormalities were not reported in the initial cohort [36] but have been observed in some patients since then (personal observation). Recently, muscle weakness was also confirmed at sarcomere level [85].

Although all the defining features of the congenital myopathies may occur in different contexts, nemaline rods are probably the histopathological feature that has been most frequently associated with non-genetic causes, many of them manifesting in adulthood and summarily referred to as sporadic late-onset nemaline myopathy (SLONM). The most frequent acquired causes include monoclonal gammopathy, HIV, and various autoimmune disorders [86,87]. The most distinguishing feature compared to genetic forms of NM is the complete absence of weakness in childhood or adolescence, and the fast rate of progression, with patients developing severe limb girdle, axial and respiratory weakness in the course of a few years. Timely recognition is essential considering that SLONM is potentially treatable, and screening for M-protein and HIV infection should therefore be part of the diagnostic work-up in cases of rapidly progressive muscle weakness in adulthood.

CONCLUSIONS

Congenital myopathies with presentation in adolescence or adulthood are of relevance to adult (neuromuscular) neurologists. In addition, improved standards of care and development of new therapies will result in an increasing number of Paediatric patients transitioning to the adult neuromuscular clinic, emphasizing the need for robust natural history data beyond childhood. Mutations in *RYR1*, the most common cause of congenital myopathies, may also give rise to “induced” and episodic manifestations presenting throughout life. Non-genetic causes ought to be considered if histopathological features, in particular nemaline rods, are unexpected in the clinical context.

KEY POINTS

Congenital myopathies may present in adulthood in particular if associated with dominant mutations in the skeletal muscle ryanodine receptor (*RYR1*), the dynamin 2 (*DNM2*), the amphiphysin 2 (*BINI*) and the Kelch Repeat-and BTB/POZ Domain-Containing Protein 13 (*KBTBD13*) gene.

Exertional rhabdomyolysis and late-onset axial myopathy are two manifestations of dominant *RYR1* mutations particularly relevant to adult neuromuscular practice that may also be associated with the malignant hyperthermia susceptibility (MHS) trait.

Reflective of improved standards of care and the advent of novel therapies, an increasing number of patients with early-onset congenital myopathies will transition to the adult neuromuscular clinic in future.

Non-genetic causes have to be considered if histopathological features, in particular nemaline rods, are unexpected in the clinical context.

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CONFLICTS OF INTEREST

The authors do not have any conflicts of interest related to this work.

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- * Series of clinical features and treatment response in 8 patients with sporadic late-onset nemaline myopathy (SLONM) associated with monoclonal gammopathy of unknown significance (MGUS).

FIGURE AND TABLES

Figure 1

The clinical spectrum of *RYR1*-related myopathies presenting in adulthood. **A)** 17-year-old male presenting with recurrent exertional rhabdomyolysis (ERM) associated with a paternally inherited heterozygous *RYR1* mutation putatively associated with Malignant Hyperthermia (MH) (reported in [26]). Note mild ptosis, often the only myopathic sign in patients presenting with *RYR1*-related ERM, and **B)** subtle scapular winging. **C-D)** Two 47-year-old patients (reported in [19, 29] with late-onset axial myopathy due dominant *RYR1* mutations. Note scapular winging and wasting of the paravertebral muscles. Although much more pronounced, these findings are similar to those shown in B), indicating a continuum between the *RYR1*-related ERM and late-onset axial myopathy spectrum. **E)** 60-year-old patient with dominantly inherited *RYR1*-related CCD (reported in [19]), showing exaggerated lumbar lordosis, mild scoliosis and tendon Achilles tightness. **F-H)** 35-year-old patient with *RYR1*-related MmD with ophthalmoparesis (reported in [19]). Note marked limitation of extraocular movements, pronounced on attempted upward gaze (G) and, to a lesser extent, abduction and adduction (F,H).

Figure 2

Histopathological features of congenital myopathies presenting in adulthood. **A)** Muscle biopsy from 60-year-old male (shown in Figure 1E) with a dominantly inherited, *RYR1*-related core myopathy (CCD). On SDH stain (transverse sections) there are predominantly well-defined central cores, but also additional smaller, more irregular and occasionally confluent core structures. **B)** Muscle biopsy from a 50-year-old male with a recessively

inherited, *RYR1*-related core myopathy (MmD). On SDH stain (transverse sections) there are multiple small cores in many fibres, often in an eccentric position.

C) Muscle biopsy from a 63-year-old female with dominantly inherited, *BIN1*-related CNM. Note increase in central nuclei on H&E stain, transverse sections. **D)** Muscle biopsy from 36-year-old female with dominantly inherited *KBTD13*-related NM. There are numerous nemaline rods appearing red on the Gomöri trichome stain, transverse sections. Rods were also prominent on Toluidine Blue-stained semithin resin sections (data not shown).

Table 1

Clinical and histopathological clues to a specific diagnosis in congenital myopathies in adults. Please note that many of the indicated features may also occur in other congenital myopathies and with different genetic backgrounds, although at lower frequency. CMS = Congenital Myasthenic Syndromes; DM1 = Myotonic Dystrophy Type 1; EDMD = Emery-Dreifuss Muscular Dystrophy; FSHD – Facioscapulohumeral Muscular Dystrophy; MFM = Myofibrillar Myopathy; SLONM = Sporadic Late Onset Nemaline Myopathy

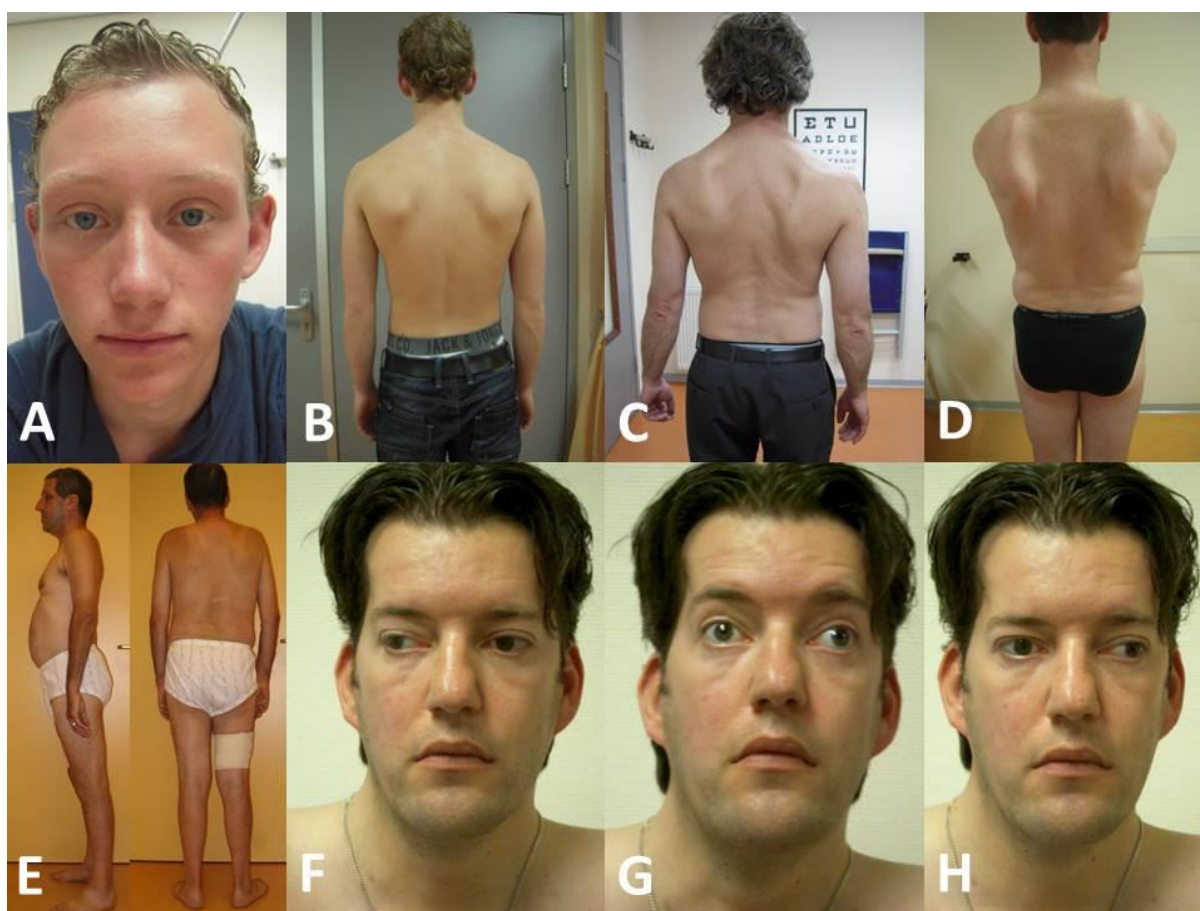


Figure 1

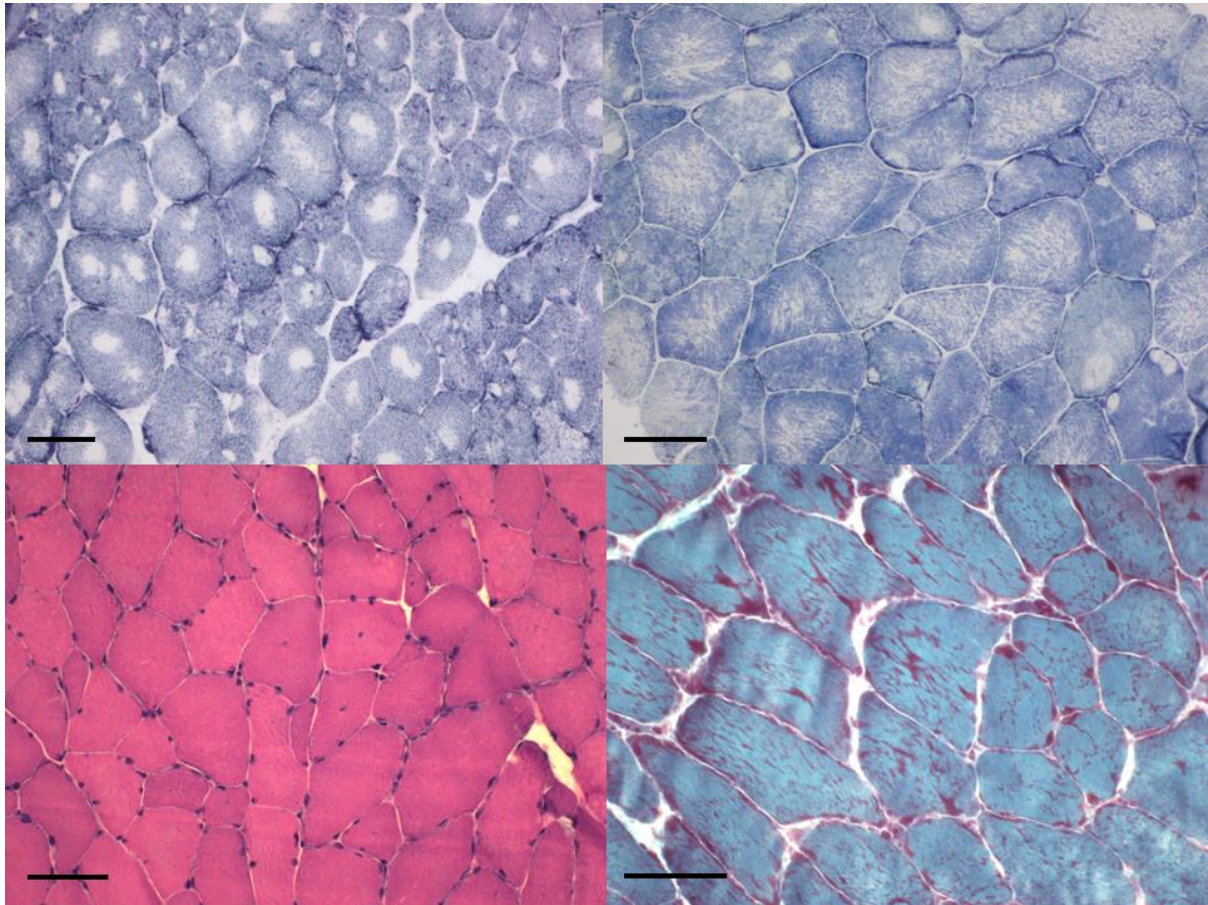


Figure 2

Feature	Congenital myopathy	Genes	Differential diagnosis
Clinical feature			
Childhood onset	CCD, MmD, NM,	<i>RYR1</i> (AR>AD), <i>NEB</i> , <i>ACTA1</i> , <i>MTM1</i> (milder cases),	CMS, DM1, mitochondrial conditions
Adult onset	CCD, CNM, NM	<i>RYR1</i> (AD>AR), <i>DNM2</i> , <i>BIN1</i> (AD), <i>KBTD13</i>	DM1, mitochondrial conditions
Facial weakness	MmD, CNM, NM	<i>RYR1</i> (AR), <i>DNM2</i> , <i>NEB</i>	DM1, CMS, mitochondrial conditions, FSHD
Ptois	CNM, MmD, CCD	<i>DNM2</i> , <i>RYR1</i>	DM1, CMS, mitochondrial conditions
EOM	MmD, CNM	<i>RYR1</i> (AR), <i>DNM2</i> , <i>MTM1</i> (mild cases, manifesting carriers)	CMS, mitochondrial conditions
Scoliosis	MmD, CNM, NM	<i>SEPNI</i> , <i>RYR1</i> , <i>NEB</i>	<i>COL6</i> -related myopathies, MFM
Rigid spine	MmD, NM	<i>SEPNI</i> , <i>MYH7</i> , <i>TTN</i> , <i>NEB</i>	<i>COL6</i> -related myopathies, EDMD, MFM
Distal weakness lower	NM, CNM, MmD	<i>NEB</i> , <i>DNM2</i> , <i>MYH7</i>	Peripheral neuropathy
Pes cavus	CNM	<i>DNM2</i>	Peripheral neuropathy
Bulbar weakness	NM, MmD	<i>NEB</i> , <i>RYR1</i> (AR)	CMS, DM1, mitochondrial conditions
Respiratory impairment	MmD, NM, CNM	<i>SEPNI</i> , <i>NEB</i> , <i>ACTA1</i> , <i>DNM2</i>	Acid maltase deficiency, mitochondrial
Cardiac involvement	MmD, NM	<i>TTN</i> , <i>MYH7</i> , (<i>ACTA1</i>), (<i>KBTD13</i>)	EDMD, mitochondrial conditions, MFM
Neuropathy	CNM	<i>DNM2</i>	Peripheral neuropathy, MFM
Malignant hyperthermia	CCD, MmD	<i>RYR1</i>	Other causes of MH
Histopathology			
Central cores	CCD	<i>RYR1</i>	Target fibres
Multi-minicores	MmD	<i>SEPNI</i> , <i>RYR1</i> (AR), <i>TTN</i> (\pm internal nuclei), <i>MYH7</i>	<i>COL6</i> -related myopathies, MFM
Central nuclei	CNM	<i>DNM2</i> , <i>BIN1</i> , <i>RYR1</i> (AR) (multiple internal), <i>TTN</i> (\pm cores)	DM1
- radial strands	CNM	<i>DNM2</i> , (<i>BIN1</i>)	
- necklace fibres	CNM	<i>MTM1</i> (mild cases, manifesting carriers), <i>DNM2</i>	
Nemaline rods	NM	<i>KBTD13</i> (\pm cores)	SLONM

Table 1